IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Lee R. Brettman, Judith A. Fox and David Edward Allison	
Application No.:	10/735,863	Group: 1644
Filed:	December 15, 2003	Examiner: Ronald B. Schwadron, Ph.D.
Confirmation No:	5328	
For:	METHOD OF ADMINISTERING AN ANTIBODY	

DECLARATION OF ERIC FEDYK UNDER 37 C.F.R. § 1.132

I, Eric Fedyk, Ph.D., declare and state the following:

1. I am the Director of Immunology and Toxicology at Millennium Pharmaceuticals, Inc. Millennium Pharmaceuticals, Inc. is the assignee of the subject patent application. My curriculum vitae is attached (Exhibit D).

2. The subject patent application claims methods for treating a human having an inflammatory bowel disease. Claim 1 states that the method comprises administering to said human an effective amount of a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for human α4β7 integrin, wherein said humanized immunoglobulin or antigen-binding fragment is administered in a single dose or in an initial dose followed by one or more subsequent doses wherein no more than about 8 mg humanized immunoglobulin or antigen-binding fragment per kg body weight are administered during a period of about one month. Claim 22 states that the method comprises administering to said human an effective amount of a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for human α4β7 integrin, wherein said humanized immunoglobulin or antigen-binding fragment is administered in a single dose or in an initial dose followed by one or more subsequent doses wherein each of said doses independently comprise an amount of humanized immunoglobulin or antigen-binding fragment thereof which is sufficient to achieve a) about 50% or greater saturation of α4β7 integrin binding sites on circulating lymphocytes and/or b) about 50% or greater inhibition of α4β7 integrin expression on the cell surface of circulating lymphocytes, and wherein said saturation and/or inhibition is maintained for a period of at least about 10 days following administration of said dose. Claim 40 states that the method comprises administering to said human an effective amount of a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for human α4β7 integrin, wherein said humanized immunoglobulin or antigen-binding fragment is administered in a single dose or in an initial dose followed by one or more subsequent doses, wherein each of said doses comprises an amount of humanized immunoglobulin or antigen-binding fragment which is sufficient to achieve and maintain a serum concentration of humanized immunoglobulin or antigen-binding

fragment of at least about 1 μg/ml for a period of at least about 10 days following administration of said dose.

3. I have read the Office Action dated October 1, 2010, and the references cited therein. I am familiar with the rejection of claims set forth in that Office Action.

4. In rejecting the claims, the Examiner cites two references by Gorden et al., that disclose the anti-alpha 4 antibody Antegren (natalizumab, also known as Tysabri®). Administration of Antegren (natalizumab) is known to be associated with an opportunistic infection of the brain, progressive multifocal leukoencephalopathy (PML), which is believed to be caused by impaired immune surveillance of the CNS, and with general immunosuppression. (See, e.g., Kent et al., 1995, Yednock et al., 1992, Coisne et al., 2009, and Tysabri® package insert 2010.)

5. Comparative *in vivo* studies of the safety and efficacy of vedolizumab (an investigational humanized antibody and of natalizumab (disclosed in the Gordon et al. references cited by the Examiner) have been completed. Vedolizumab binds to α4β7 integrin and contains the six CDRs specified in claim 1. (Versions of antibodies which contain the six CDRs have been known as LDP-02, MLN02, MLN0002.) The results show that vedolizumab has a superior safety profile and benefit/risk ratio in inflammatory bowel disease compared to natalizumab. These studies and the results of the studies are described below.

IMMUNE SURVEILLANCE OF THE CNS

6. The effects of vedolizumab and natalizumab on immune surveillance of the CNS were analyzed in a Rhesus macaque model of experimental autoimmune encephalomyelitis (EAE). EAE is a leukoencephalopathy which, like PML, results from immune surveillance of the CNS ('t Hart 2005). The Rhesus monkey model was selected for this study because it is an established primate EAE model in which both vedolizumab and natalizumab are pharmacologically active.

7. In this model, animals are sensitized to myelin/oligodendrocyte glycoprotein (MOG) by subcutaneous immunization with recombinant human MOG. This sensitizes the adaptive immune response to the MOG autoantigen in the skin, and the resulting memory T lymphocytes circulate and survey additional organs for the presence of MOG. MOG antigens are expressed endogenously by oligodendrocytes in the CNS and are recognized by the sensitized anti-MOG T lymphocytes, which initiates an autoimmune response that culminates in EAE ('t Hart 2005). Normal immune surveillance of the CNS induces EAE in this model.

8. In the study, there were three treatment groups i) vehicle (i.e., negative control that develops EAE), ii) vedolizumab treated, and iii) natulizumab treated. Because normal immune surveillance of the CNS induces EAE in this model, the development of EAE in animals that are treated with vedolizumab or natulizumab indicates that the antibody does not impair CNS immunosurveillance. Conversely, a delay in EAE induction as compared to vehicle control indicates that the antibody impairs CNS immunosurveillance and, therefore, treatment with that antibody is a risk factor for PML.

9. The animals (7 or 8 per group) received an initial intravenous bolus of vehicle control, 30 mg/kg natulizumab or 30 mg/kg vedolizumab before subcutaneous immunization with recombinant human myelin/oligodendrocyte glycoprotein (rhMOG). Following the initial treatment and immunization with rhMOG, the animals received vehicle, natulizumab or vedolizumab by intravenous bolus, at the same doses, once weekly.

10. The primary assessment of immune surveillance of the CNS was the degree of inflammation in the CNS, as measured by: i) clinical scores of EAE, ii) levels of leukocytes in the cerebrospinal fluid (CSF), iii) magnetic resonance imaging (MRI) of brain hemispheres, iv) histopathology of brain tissue, and v) leukocytosis of the vasculature. (Exhibit A)

11. Fifty percent (4 of 8) of vehicle dosed animals and 57% (4 of 7) of vedolizumab treated animals developed clinical symptoms of EAE in their respective groups, whereas only 14% (1 or 7) of natulizumab treated animals developed symptoms of EAE within their groups. (Exhibit A: FIG. 1). The mean magnitude of EAE clinical scores was significantly ($p<0.05$) higher and the mean time of onset of clinical symptoms were significantly ($p<0.05$) longer in the natalizumab group as compared to the respective means of animals in the vehicle control group.

12. The level of leukocytes in the CSF was assessed to determine immune surveillance of the CNS. CSF was collected via the cisterna magna from animals prior to treatment with vehicle or antibody, 1 and 2 weeks after initial treatment, and at necropsy. Normal immune surveillance of the CNS is demonstrated by increases in the level of leukocytes in the CSF in this model. Conversely, impaired CNS immune surveillance is indicated by no increase in the level of leukocytes in the CSF. An increase in the level of white blood cells (WBCs) in the CSF was observed in animals that developed EAE as compared to their pre-treatment levels, however high inter-individual variation in levels of WBCs in the CSF prevented attaining a significant difference between the the means of vehicle control and natalizumab groups ($p=0.09$). The mean values of WBCs in the CSF of the vehicle control and the vedolizumab-treatment groups were higher at necropsy than at pre-treatment sampling. In contrast, the mean value of WBCs in the CSF of the natulizumab group was unchanged from pre-treatment sampling. (Exhibit A: FIG. 2)

13. The clinical symptoms of rhesus EAE result from inflammation and demyelinating lesions in cerebral white matter that are initiated by autoreactive helper T lymphocytes ('t Hart 2005). These pathologic changes were quantified by blinded observers, using MRI of formalin-fixed brain hemispheres of rhesus monkeys. T2-weighted, quantitative T2 relaxation time image maps and magnetization transfer ratio (MTR) image maps were utilized to measure inflammation and demyelination. The presence of white matter lesions was qualitatively graded between 0 (no lesions in white matter structures) and 10 (total white matter is affected by the lesion). Higher scores thus indicated more lesions, more severe EAE, and therefore more immune surveillance of the CNS in this model.

14. The mean values for lesion loads in brain hemispheres from the vehicle and vedolizumab groups were similar, and were significantly ($p<0.05$) higher than the mean value observed for the natulizumab group. These results indicate that immune surveillance of the CNS comparable between the vehicle and vedolizumab groups, but was impaired in the natulizumab group. (Exhibit A: FIG. 3)

15. Tissue sections from the formalin-fixed hemispheres that were analyzed by MRI were analyzed microscopically to histologically further define the nature of the observed lesions. Representative photomicrographs are included in Exhibit A: Figure 4. Qualitatively comparable demyelination was observed in the white matter of vehicle control animals (Figure 4 A and D) and vedolizumab animals (Figure 4 C and F), but not in natalizumab animals (Figure 4 B and D). Qualitatively comparable inflammation was observed in the white matter of vehicle control animals (Figure 4 G and J) and vedolizumab animals (Figure 4 I and L), but not in natalizumab animals (Figure 4 H and K).

16. The extent of inflammation and demyelination in tissue sections was qualitatively scored by a blinded anatomic pathologist. The composite group mean inflammation and demyelination score was significantly lower in the natalizumab group than in the vehicle group (0.1 ± 0.1 versus 1.4 ± 0.4; $p = 0.0098$). The individual mean inflammation and demyelination scores for the vedolizumab group appear comparable to those for the vehicle group (Exhibit A: Figure 5).

17. The histology analysis concurred with the independent MRI analysis. A comparison of the MRI score to the histologic inflammation or histologic demyelination score for each individual animal yielded coefficients of variation (R^2) of 0.83 and 0.89, respectively (data not shown).

18. Levels of total leukocytes and various leukocyte subsets in the vasculature were monitored during the investigation as an inverse indicator of immune surveillance of peripheral tissue. The natulizumab treated animals exhibited a significant ($p<0.05$) vascular leukocytosis and lymphocytosis as compared to the vehicle group. The leukocytosis consisted of significant ($p<0.05$) elevations in monocytes, lymphocytes, basophils, and eosinophils, but not neutrophils. The lymphocytosis consisted of significant ($p<0.05$) elevations in total T lymphocytes, total and memory helper T lymphocytes, total and memory cytotoxic T lymphocytes, and total B lymphocytes, but not NK cells. In contrast, no differences in leukocyte count, erythrocyte count, reticulocyte count, platelet count, and differential counts of neutrophils (segmented), lymphocytes, monocytes, eosinophils, and basophils were observed between the vedolizomab-treated animals and the vehicle-treated animals. Moreover, no differences between the vedolizomab group and the vehicle group were observed by flow cytometry analysis of lymphocyte subpopulations, most notably total B lymphocytes, total T lymphocytes, helper T lymphocytes, cytotoxic T lymphocytes, memory helper T lymphocytes, memory cytotoxic T lymphocytes, and NK cells. (Exhibit A: FIG. 6)

19. Target occupancy in the monocyte, naïve and memory helper T lymphocyte, and naïve and memory cytotoxic T lymphocyte populations in peripheral blood was also analyzed by flow cytometry for each animal. The $\alpha 4\beta 7$ integrin was saturated for the duration of the experiment in each animal exposed to vedolizumab. For example, the a4b7 integrin is detected on approximately 20% to 40% of memory helper T lymphocyte population in peripheral blood prior to exposure to vedolizumab and in contrast, less than 3% of these populations at trough exposures of vedolizumab on Days 7, 14, and 21. In contrast, approximately 15% to 38% of memory helper T lymphocytes in peripheral blood exposed to vehicle expressed unbound $\alpha 4\beta 7$ integrin at the corresponding time points. (Exhibit A: FIG. 7). These data demonstrate that the

absence of an effect of vedolizumab on immune surveillance of the CNS is not explained by a failure to saturate the intended target for the duration of the investigation.

20 The results of this study demonstrate that vedolizumab has a superior safety profile in comparison to natalizumab in this animal model, in particular that vedolizumab does not impair surveillance of the CNS. This was observed even though $\alpha 4\beta 7$ integrins were continuously saturated by vedolizumab during the course of the study. In contrast, this study confirmed prior studies showing that similar doses of natulizumab impaired immune surveillance of the CNS. (Kent 1995, Yednock 1992, Coisne 2009, DSD-01250, DSD-01363, and Tysabri® package insert 2010). These results suggest that, in contrast to treatment with natalizumab, treatment with vedolizumab may not be a risk factor for PML.

Safety Comparison of Vedolizumab and Natalizumab

21. Three separate investigations were designed and conducted in Cynomolgus monkeys to compare the safety of vedolizumab and natalizumab. The first two studies independently assessed the affects of vedolizumab and natalizumab on the immune system. The third investigation was a head to head comparison of the safety profiles of vedolizumab and natalizumab.

22. The animals were evaluated for changes in clinical signs (twice daily cage side observations, post dose observations, weekly detailed examinations, food consumption, weekly body weight) in all investigations, electrocardiograms and ophthalmic examinations in subchronic and chronic investigations. Blood samples were collected pre- and post-dose for evaluation of pharmacokinetics, pharmacodynamics, primate anti-human antibodies in all investigations and T-dependent antigen response (TDAR) in the single dose, subchronic and head to head comparison investigations. At termination, a full necropsy was conducted on all animals, 50 different tissues were collected, preserved, processed, stained with hematoxylin and eosin, and examined microscopically by an American College of Veterinary Pathologists-certified, anatomic pathologist and peer-reviewed independently in single-dose, subchronic and chronic investigations.

<u>Vedolizumab effects on the innate and adaptive immune systems</u>

23. Subchronic and chronic (3 months and 6 months exposure, respectively) toxicology investigations of vedolizumab included assessment of potential effects on the innate immune system (natural killer cell activity) and the adaptive immune system (T cell dependent antigen response (TDAR) to keyhole limpet hemocyanin (KLH)). Healthy, purpose-bred, experimentally naive cynomolgus monkeys (males and females), received vehicle control, 10 mg/kg vedolizumab, 30 mg/kg vedolizumab or 100 mg/kg vedolizumab for 12 or 26 consecutive weeks by a 20-minute intravenous infusion every other week, and a subset of animals were studied for another one or three months post last dose, respectively.

24. Vedolizumab administered weekly or bi-weekly to cynomolgus monkeys for 3, 13 or 26 consecutive weeks at dosages of 10, 30, or 100 mg/kg was well tolerated. Vedolizumab did not elicit changes in clinical observations, food consumption values, electrocardiologic assessments, ophthalmologic assessments, clinical pathology parameters (i.e. serum chemistry,

hematology, coagulation, and urinalysis), cerebrospinal fluid evaluations, and postmortem organ weight and necropsy data. Animals dosed at 100 mg/kg in the chronic investigation were exposed to vedolizumab for up to nine months because the $\alpha 4\beta 7$ integrin remained saturated throughout the three month post-dose recovery period. The no-observed-adverse effect level for vedolizumab administered chronically was determined to be at least 100 mg/kg, the highest dose examined.

25. After administration of the first dose, the exposure to vedolizumab (as measured by either Cmax or AUC) increased in serum as the dose increased, with the increase tending to be approximately dose-proportional (Exhibit B-Figure 1A). After administration of the last dose in the subchronic and chronic investigations, the exposure to vedolizumab increased as the dose increased; however, the increase was more than dose-proportional (Table 1) because of the emergence of primate anti-human antibody (PAHA) that was more prevalent at the lower dose levels. PAHA responses in the subchronic investigation were first detectable after day 8 in the 10 mg/kg group and at day 29 for the 30 and 100 mg/kg groups (Exhibit B-Figure 1B).

Table 1 Exposure Levels Of Vedolizumab In Cynomolgus monkeys.

	10 mg/kg				30 mg/kg				100 mg/kg			
	Day 1		Day 85		Day 1		Day 85		Day 1		Day 85	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Tmax (hr)	0.5	0.1	0.6	0.2	0.6	0.2	1.2	2.2	1.8	3.4	1.2	1.3
Cmax (ug/mL)	300	66.3	150	172	911	450	902	377	3010	729	5070	875
AUC0-168hr (ug*hr/mL)	22,500	1820	12,100	18,500	72,400	19,600	71,700	58,300	255,000	39,300	490,000	89,300
AUC0-336hr (ug*hr/mL)	32,500	4690	28,400	35,800	117,000	30,900	110,000	122,000	406,000	60,700	834,000	142,000
AUC0-2184hr (ug*hr/mL)	N/A	N/A	55,600	73,400	N/A	N/A	190,000	240,000	N/A	N/A	1,570,000	326,000
N/A: Not Applicable												

26. Target saturation by vedolizumab was quantified by flow cytometric analysis of the GI-homing ($\alpha 4\beta 7^+$) memory ($CD45RA^-$), helper ($CD4^+$) T lymphocyte population within peripheral blood samples. The mean percentage of cells with unbound $\alpha 4\beta 7$ integrin in the memory helper T lymphocyte population pre-exposure, was 27-29% across all dose groups and these percentages decreased to less than 0.2% after exposure to vedolizumab, for at least 300 hours (Exhibit B- Figure 1C).

27. Immunohistochemical analyses of cecum from animals chronically exposed to vedolizumab revealed a reduction in the staining intensity and frequency of mononuclear cells expressing beta 7 integrins in the submucosal tissue of animals exposed to vedolizumab as

compared to vehicle controls (Exhibit B- Figure 1D and 1E). A concomitant elevation in levels of GI-homing, memory helper T lymphocytes was consistently observed in peripheral blood of animals dosed with vedolizumab. The mean percentage of these lymphocytes prior to exposure to vedolizumab in the subchronic investigation was 27.8%, 24.3%, and 19.3% in the 10, 30, and 100 mg/kg groups, respectively (Exhibit B- Figure 1F). These percentages increased 2 to 3-fold, after 7 and 14 days of exposure to vedolizumab, reaching highs of 54.6%, 54.1%, and 46.1%, respectively (Exhibit B- Figure 1F), despite the level of other leukocyte subsets, including the total memory helper population, remaining unchanged. This pharmacodynamic (PD) response was initially observed in all animals dosed with vedolizumab, however it decreased in some animals at trough concentrations of vedolizumab from day 15 onward (Exhibit B- Figure 1F) and ultimately was absent in 7 of 12 animals in the 10 mg/kg group by day 29, and 11 of 12 animals by days 57 and 85. In the 30 mg/kg group, the PD response waned in 6 of 12 animals at trough concentrations of vedolizumab on days 57 and 85. In the 100 mg/kg group, the PD response disappeared in 3 of 12 animals at days 57 and 85. The diminution of the PD response of these animals primarily at lower doses, coincided with the existence of a PAHA response to vedolizumab, indicating that the pharmacologic activity of vedolizumab was neutralized by PAHA in that animal. Therefore, all subsequent analyses only include data from animals that exhibited a PD response in the gut-homing, memory helper T lymphocyte population at that time point.

28. Comprehensive histomorphologic evaluation of 50 different tissues from each animal exposed to vedolizumab in subchronic and chronic investigations revealed only gastrointestinal-tropic effects. Vedolizumab induced minimal to mild lymphoid depletion in the Peyer's patches of the gastrointestinal tract in male animals at 30 and 100 mg/kg (Table 2). There were no other vedolizumab associated alterations in morphology in any tissue in these animals (Table 2).

Table 2: Macroscopic and Histomorphologic Effects of Vedolizumab on Tissues of Cynomolgus monkeys from subchronic and chronic investigations.

	Macroscopic Effect		**Histomorphologic Effect***	
Tissue	**3 month**	**6 month**	**3 month**	**6 month**
Adrenals	None	None	None	None
Aorta (thoracic)	None	None	None	None
Bone and marrow (sternum)	None	None	None	None
Bone and marrow (distal femur including articular surface)	None	None	None	None
Brain (cerebrum, cerebellum, midbrain and medulla oblongata)	None	None	None	None
Cecum	None	None	None	None
Colon	None	None	None	None
Duodenum	None	None	None	None
Epididymides	None	None	None	None
Esophagus	None	None	None	None
Eyes	None	None	None	None

Gallbladder	None	None	None	None
Heart (including section of aorta)	None	None	None	None
Ileum	None	None	Atrophy of Peyer's Patches	Atrophy of Peyer's Patches
Injection site /infusion site (from the last site of injection)	None	None	None	None
Jejunum	None	None	None	None
Kidneys	None	None	None	None
Lacrimal glands	None	None	None	None
Larynx (1 level)	None	None	None	None
Liver (sample of 2 lobes)	None	None	None	None
Lungs (including bronchi)	None	None	None	None
Lymph nodes (mandibular, politeal –bilateral, mesenteric)	None	None	None	None
Mammary gland (ventral thoracic)	None	None	None	None
Nasal cavity/turbinates (1 level)	None	None	None	None
Optic nerves	None	None	None	None
Ovaries	None	None	None	None
Oviducts	None	None	None	None
Pancreas	None	None	None	None
Pharynx	None	None	None	None
Pituitary	None	None	None	None
Prostate	None	None	None	None
Rectum	None	None	None	None
Salivary glands (mandibular)	None	None	None	None
Sciatic nerve	None	None	None	None
Seminal vesicles	None	None	None	None
Skeletal muscle (thigh)	None	None	None	None
Skin and subcutis(ventral thoracic)	None	None	None	None
Spinal cord (cervical, thoracic, lumbar)	None	None	None	None
Spleen	None	None	None	None
Stomach	None	None	None	None
Testes	None	None	None	None
Thymus	None	None	None	None
Thyroid lobes (and parathyroids)	None	None	None	None
Tongue	None	None	None	None
Trachea	None	None	None	None
Urinary bladder	None	None	None	None
Uterus (cervix and body)	None	None	None	None
Vagina	None	None	None	None
* Tissues from all animals were embedded in paraffin wax, sectioned, stained with hematoxylin and eosin, and were examined histopathologically by two AVCP-certified pathologists (ie. peer-reviewed data).				

29. The PD response to vedolizumab in peripheral blood in the subchronic, chronic and head to head investigations was restricted to gut-homing, memory helper T lymphocytes (Exhibit B- Figure 1F). Vedolizumab did not affect larger subpopulations of leukocytes including: total leukocytes (Exhibit C- Figure 2A) lymphocytes (Exhibit C- Figure 2B), neutrophils, monocytes, basophils and eosinophils (Exhibit C- Figure 2C) and T lymphocytes, memory helper T lymphocytes, memory cytotoxic T lymphocytes, B lymphocytes and NK cells (Exhibit C- Figure 2D).

30. In contrast, natalizumab elicited a broader PD profile which included significant ($p < 0.05$) vascular leuko- and lymphocytoses in a head to head comparison with vedolizumab (Exhibit C- Figures 2A and B). The natalizumab-induced leukocytosis consisted of significant ($p<0.05$) elevations in monocytes, lymphocytes, basophils and eosinophils, but not neutrophils (Exhibit C- Figure 2C). The natalizumab-induced lymphocytosis consisted of significant ($p<0.05$) elevations in total T lymphocytes, total and memory helper T lymphocytes, total and memory cytotoxic T lymphocytes and total B lymphocytes, but not natural killer cells (Exhibit C- Figure 2D).

31. Potential effects of vedolizumab on systemic adaptive immunity were evaluated by examining the systemic T cell dependent antibody response (TDAR), a cumulative assessment of dendritic cell, B and T lymphocyte function *in vivo*. A primary TDAR was induced during the third month of exposure to vedolizumab in the subchronic investigation, by immunizing with a neoantigen, keyhole limpet hemocyanin (KLH). Animals dosed with vedolizumab at 30 or 100 mg/kg mounted primary IgM and IgG TDARs to KLH which were comparable to vehicle controls and there were no significant differences in group mean anti-KLH IgM (Exhibit C- Figure 3A) or IgG (Exhibit C- Figure 3B) TDARs as compared to the means of the vehicle control group.

Effects of natalizumab on systemic immune responses

32. A single-dose, GLP investigation of the effect of natalizumab (Biogen Idec Inc., Cambridge MA) on systemic immune responses in Cynomolgus monkeys was assessed. Healthy, purpose-bred, experimentally naive cynomolgus monkeys (males and females), received one 20-minute intravenous infusion of vehicle control, 10 mg/kg natalizumab or 30 mg/kg natalizumab.

33. Potential effects of natalizumab on systemic adaptive immunity were evaluated by examining the systemic T cell dependent antibody response (TDAR), a cumulative assessment of dendritic cell, B and T lymphocyte function *in vivo*. Animals exposed to a single dose of natalizumab at 10 or 30 mg/kg in contrast did not mount primary anti-KLH IgM TDARs which were comparable to vehicle controls (Exhibit C- Figure 3C), despite mounting anti-KLH IgG primary responses (Exhibit C- Figure 3D). The magnitude of the mean primary anti-KLH IgM TDAR in the 30 mg/kg group was significantly ($p<0.05$) lower at day 16 than the mean response of the vehicle group (Exhibit C- Figure 3C), whereas comparable differences were not observed on the primary anti-KLH IgG TDAR (Exhibit F- Figure 3D).

Head to head comparison of vedolizumab and natalizumab

34. A head to head comparison of the effects of vedolizumab and natalizumab on recall TDAR responses in Cynomolgus monkeys was also conducted. Healthy, purpose-bred, experimentally naive cynomolgus monkeys (males and females), received three 20-minute intravenous infusions of vehicle control, 30 mg/kg natalizumab or 30 mg/kg vedolizumab once a week, for three weeks.

35. Potential effects on a recall TDAR response were assessed in the head to head investigation by injecting the tetanus toxoid (TT) antigen subcutaneously into animals, 14 days prior to dosing, and then challenging with TT following initial dosing with vehicle control, vedolizumab (30 mg/kg) or natalizumab (30 mg/kg) and measuring recall IgM and IgG TDAR, 10 to 20 days after challenge with TT. The vehicle, vedolizumab and natalizumab groups mounted mean anti-TT IgM recall responses which were of comparable magnitude; 1.0 to 1.3-fold, 1.0 to 3.0-fold and 0.8 to 1.9-fold on days 10, 12 14 and 16 as compared to the corresponding day 1 baselines, respectively (Exhibit C- Figure 3E). The vehicle, vedolizumab and natalizumab groups also mounted comparable mean anti-TT IgG recall responses; 1.0 to 4.9-fold, 1.0 to 3.6-fold and 1.0 to 3.0-fold on days 14, 16, 18 and 20 as compared to the corresponding day 1 baselines, respectively (Exhibit C- Figure 3F). There were no significant differences in the gross magnitude or frequency of anti-TT IgM (Exhibit C- Figure 4C) or IgG (Exhibit C- Figure 4D) TDAR between the vedolizumab, natalizumab and vehicle control groups. No significant effects of vedolizumab or natalizumab were observed on NK cell function (Exhibit C- Supplemental Figures 1A and B), despite expression of low levels of the $\alpha 4\beta 7$ integrin by this subset of leukocytes.

36. These studies showed that vedolizumab did not affect organs and tissues outside of the GI tract. Vedolizumab was also shown to have no effect on systemic adaptive immune responses, as measured by the TDAR. In contrast, treatment with natalizumab elicited a broad peripheral blood leukocytosis and lymphocytosis in Cynomolgus monkeys, which consisted of elevations in monocytes, basophils, eosinophils, total T lymphocytes, total and memory helper T lymphocytes, total and memory cytotoxic T lymphocytes and total B lymphocytes, and suppressed primary IgM TDAR.

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37. All statements made herein of my own knowledge are true, all statements made herein on information and belief are believed to be true, and these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and may jeopardize the validity of the application or any patent issuing thereon.

Eric Pedyk

Date: 27 JAN 2011

EXHIBIT A

Figure 1 Occurrence and Onset of EAE Symptoms

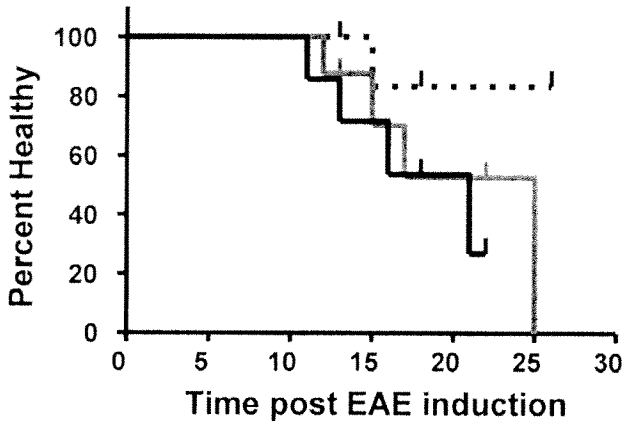
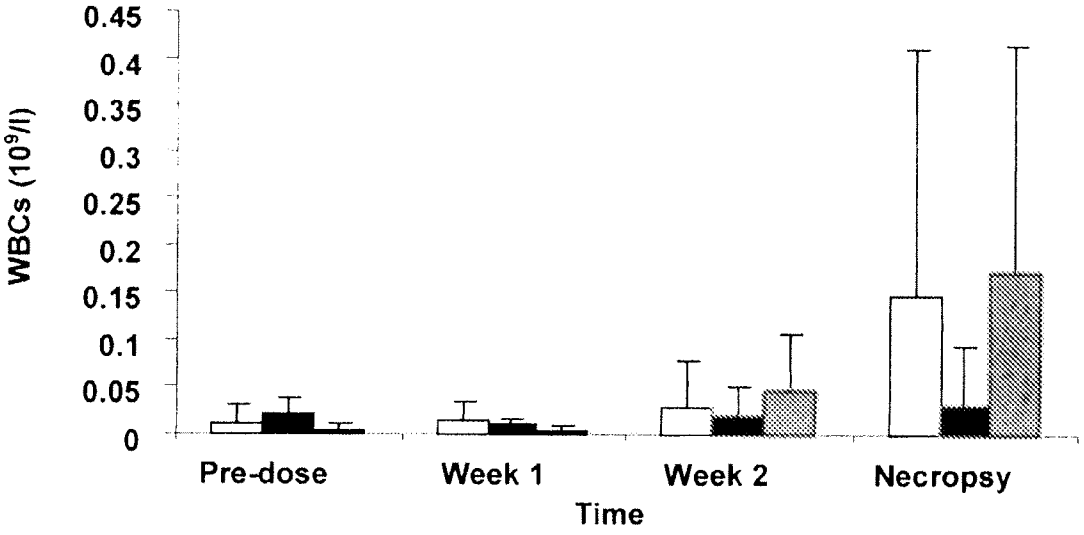


Figure 1 Animals received an initial intravenous (IV) bolus of vehicle (grey bars), natalizumab at 30 mg/kg (checked bars), or vedolizumab at 30 mg/kg (solid black bars) before subcutaneous (SC) immunization with recombinant human myelin/oligodendrocyte glycoprotein (rhMOG) to induce experimental autoimmune encephalomyelitis (EAE) and were dosed with vehicle or test article once weekly (QW) thereafter.

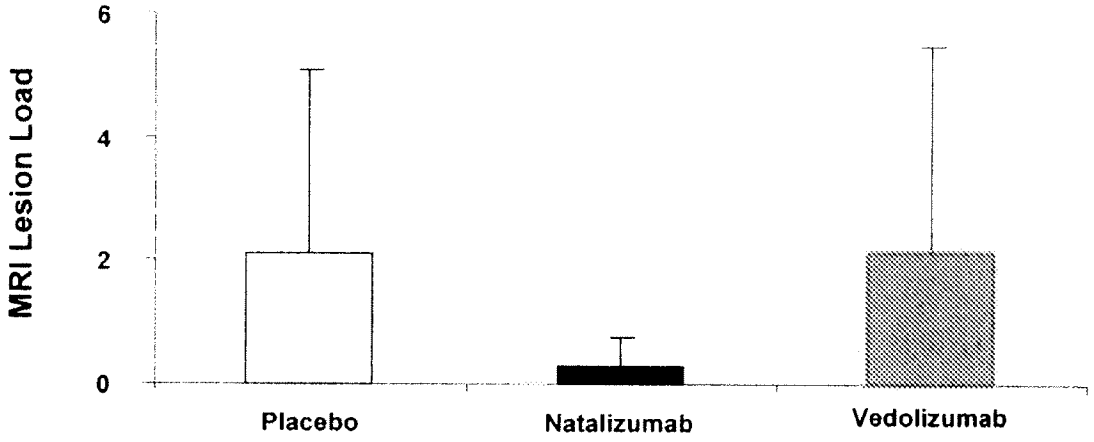
Figure 2 Natalizumab and Not Vedolizumab Delayed Onset of Leukocytic Infiltrates in the Cerebrospinal Fluid of Rhesus Macaques



Source: Report RPT-01673.

Figure 2 Animals received an initial intravenous (IV) bolus of vehicle (white bars), natalizumab at 30 mg/kg (black bars), or vedolizumab at 30 mg/kg (grey bars) before subcutaneous (SC) immunization with recombinant human myelin/oligodendrocyte glycoprotein (rhMOG) to induce experimental autoimmune encephalomyelitis (EAE), and were dosed with test article once weekly (QW) thereafter. Cerebrospinal fluid (CSF) was collected via the cisterna magna from deeply sedated or euthanized monkeys at the indicated time points post-immunization. Automated white blood cell (WBC) counts were obtained with a hematology analyzer. Data are the mean values and standard deviations (SD) for vehicle (n = 8), natalizumab (n = 7), and vedolizumab (n = 7).

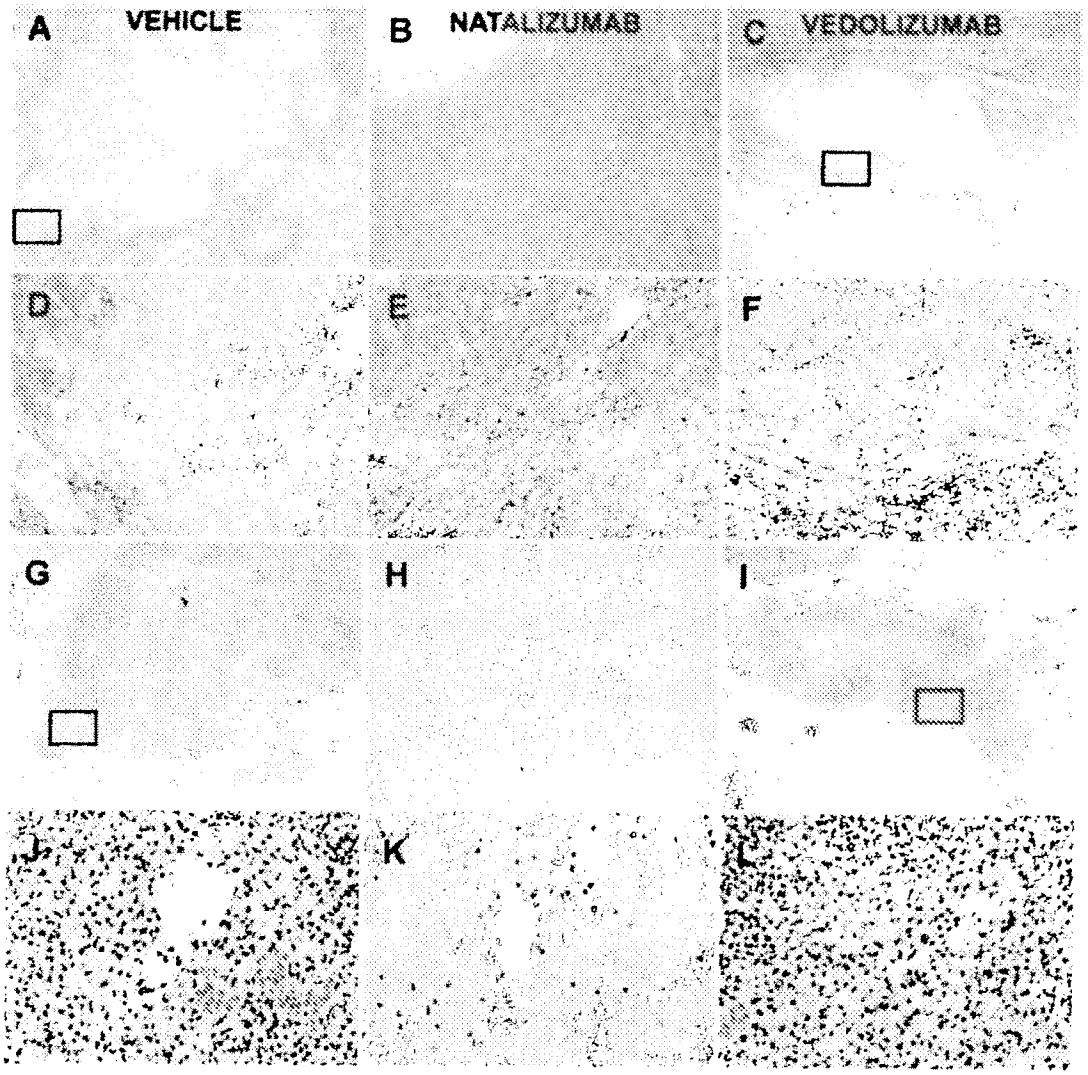
Figure 3 **Lower Load of Total Lesions in Brain Hemispheres of Rhesus Macaques Dosed With Natalizumab**



Source: Report RPT-01673.

Figure 3 Animals received an initial intravenous (IV) bolus of vehicle, natalizumab (30 mg/kg), or vedolizumab (30mg/kg) before subcutaneous (SC) immunization with recombinant human myelin/oligodendrocyte glycoprotein (rhMOG) to induce experimental autoimmune encephalomyelitis (EAE), and were dosed once weekly (QW) thereafter with test article. Postmortem magnetic resonance imaging (MRI) was performed on a brain hemisphere from each animal. The presence of white matter lesions was qualitatively graded between 0 (no lesions in white matter structures) and 10 (total white matter is affected by the lesion) by a neurologist who was blinded to the treatment each animal had received. Data are the mean values and standard deviations (SD) for the vehicle (n = 8), natalizumab (n = 7), and vedolizumab (n = 7) groups.

Figure 4 Representative Photomicrographs Illustrating That Vedolizumab Did Not Prevent Cerebral Demyelination or Inflammation



Three blocks of tissue were excised from each hemisphere analyzed by magnetic resonance imaging (MRI), from approximately the same region for all animals. Paraffin sections were stained with Kluwer Barrera (A-F) or hematoxylin and eosin (G-L) histochemical stains. Photomicrographs A-C and G-I are at 25× and D-F and J-L are at 250× magnification. Boxes depicted in A, C, G, and I highlight the regions of tissue from which the higher magnification images D, F, J, and L were derived. Representative images are shown.

Figure 5 Pathology Assessment Illustrating That Vedolizumab Did Not Prevent Cerebral Inflammation or Demyelination

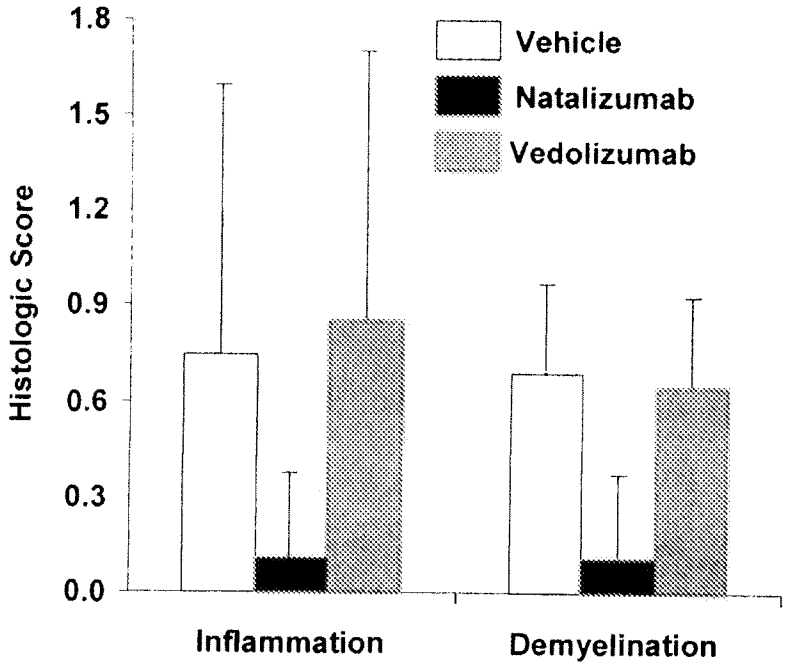
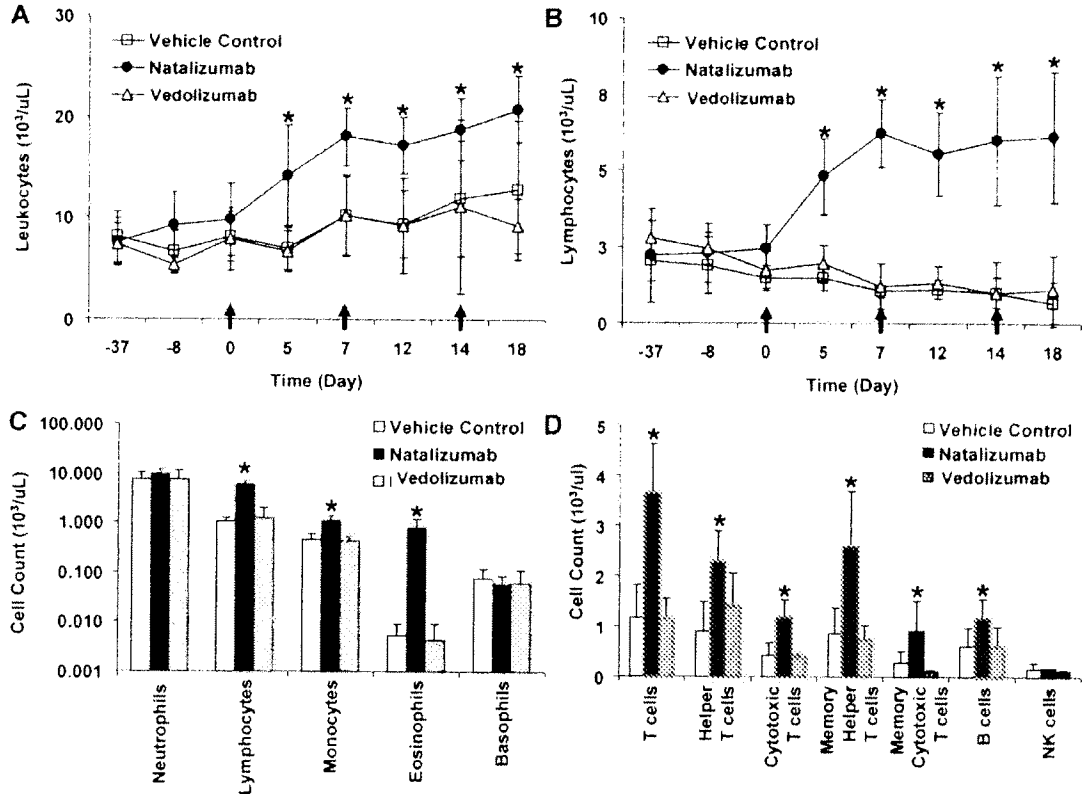


Figure 5 Three blocks of tissue were excised from each hemisphere analyzed by magnetic resonance imaging (MRI), from approximately the same region for all animals. Paraffin sections were stained with hematoxylin and eosin, Kluwer Barrera, and Bielschowsky's silver stains. For calculation of group means and statistical analyses of histopathology, the ordered qualitative outcomes were converted to quantitative discrete outcomes (ie, +/– = 0.5; +/– to + = 0.75; + = 1; ++ = 2). Data are the mean values and standard deviations (SDs) for the vehicle (n = 8), natalizumab (n = 7), and vedolizumab (n = 7) groups.

Figure 6 Natalizumab Induces a Generalized Vascular Leukocytosis in Rhesus Monkeys That is not Observed With Vedolizumab



Peripheral blood was drawn from animals pre- (Days –37, -8 and 0) and post-(5, 7, 12, 14 and 18) exposure to vehicle, natalizumab at 30 mg/kg, or vedolizumab at 30 mg/kg (arrows). Animals also received a subcutaneous (SC) immunization with recombinant human myelin/oligodendrocyte glycoprotein (rhMOG) on Day 0 to induce experimental autoimmune encephalomyelitis (EAE). Natalizumab, but not vedolizumab, increased the absolute count of leukocytes (A) and lymphocytes (B) after exposure (Days 5, 7, 12, 14 and 18) as compared to pre-exposure, baseline levels (Days –37, -8 and 0). (C) Natalizumab but not vedolizumab elevated the level of monocytes, lymphocytes, and eosinophils in peripheral blood after 12 days of exposure. (D) Natalizumab but not vedolizumab elevated the calculated levels of total T lymphocytes ($CD3^+$), helper T lymphocytes ($CD3^+CD4^+$), cytotoxic T lymphocytes ($CD3^+CD8^+$), memory helper T lymphocytes ($CD3^+CD4^+CD45RA^-$), memory cytotoxic T lymphocytes ($CD3^+CD8^+CD45RA^-$), and B lymphocytes ($CD20^+$), but not natural killer (NK) cells ($CD3^-CD16^+$) after 12 days of exposure. Cell Count = absolute lymphocyte count × percent of lymphoid gate. All histograms display the mean and standard deviation for each group (n = 7 or 8). * denotes a significant difference ($p < 0.05$) relative to vehicle control on that day.

Figure 7 The $\alpha_4\beta_7$ Integrins Expressed by Memory Helper T Lymphocytes in Peripheral Blood Were Saturated by Vedolizumab for the Duration of the Investigation in Each Animal Exposed to Vedolizumab

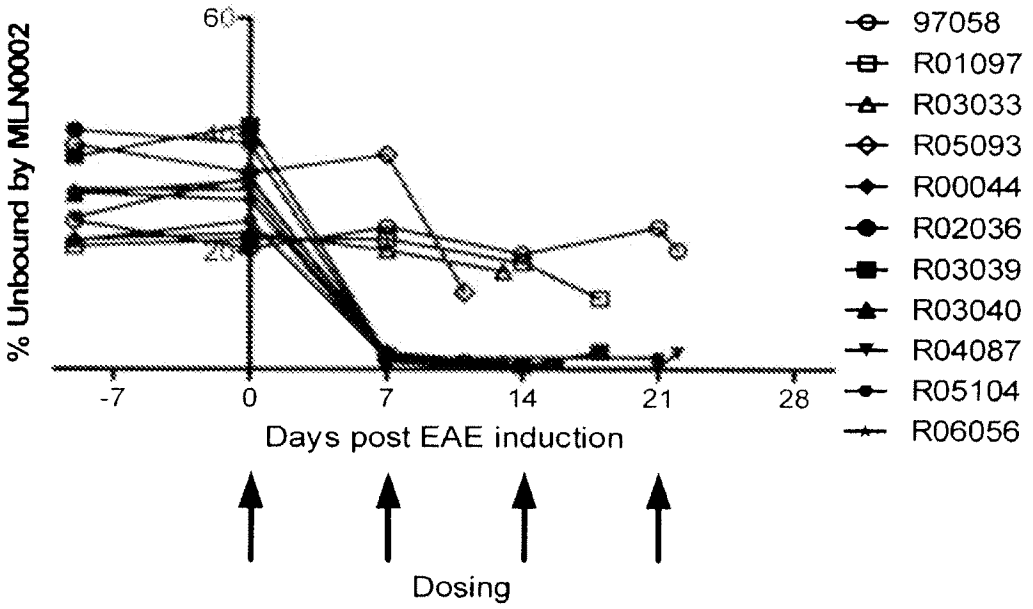


Figure 7 Peripheral blood was drawn from animals on Days −10, 0, 7, 14, and 21 before an intravenous (IV) bolus of vehicle (open symbols) or Vedolizumab at 30 mg/kg (closed symbols) on Days 0, 7, and 14. Animals also received a subcutaneous (SC) immunization with recombinant human myelin/oligodendrocyte glycoprotein (rhMOG) on Day 0 to induce experimental autoimmune encephalomyelitis (EAE). Saturation of the $\alpha_4\beta_7$ integrin expressed by the memory helper T lymphocyte population ($CD3^+CD4^+CD45RA^-$ lymphocytes) was then measured ex vivo by flow cytometry. Data represent the percentage of the population expressing unsaturated $\alpha_4\beta_7$ integrin and are values for samples from individual animals at that time point.

EXHIBIT B

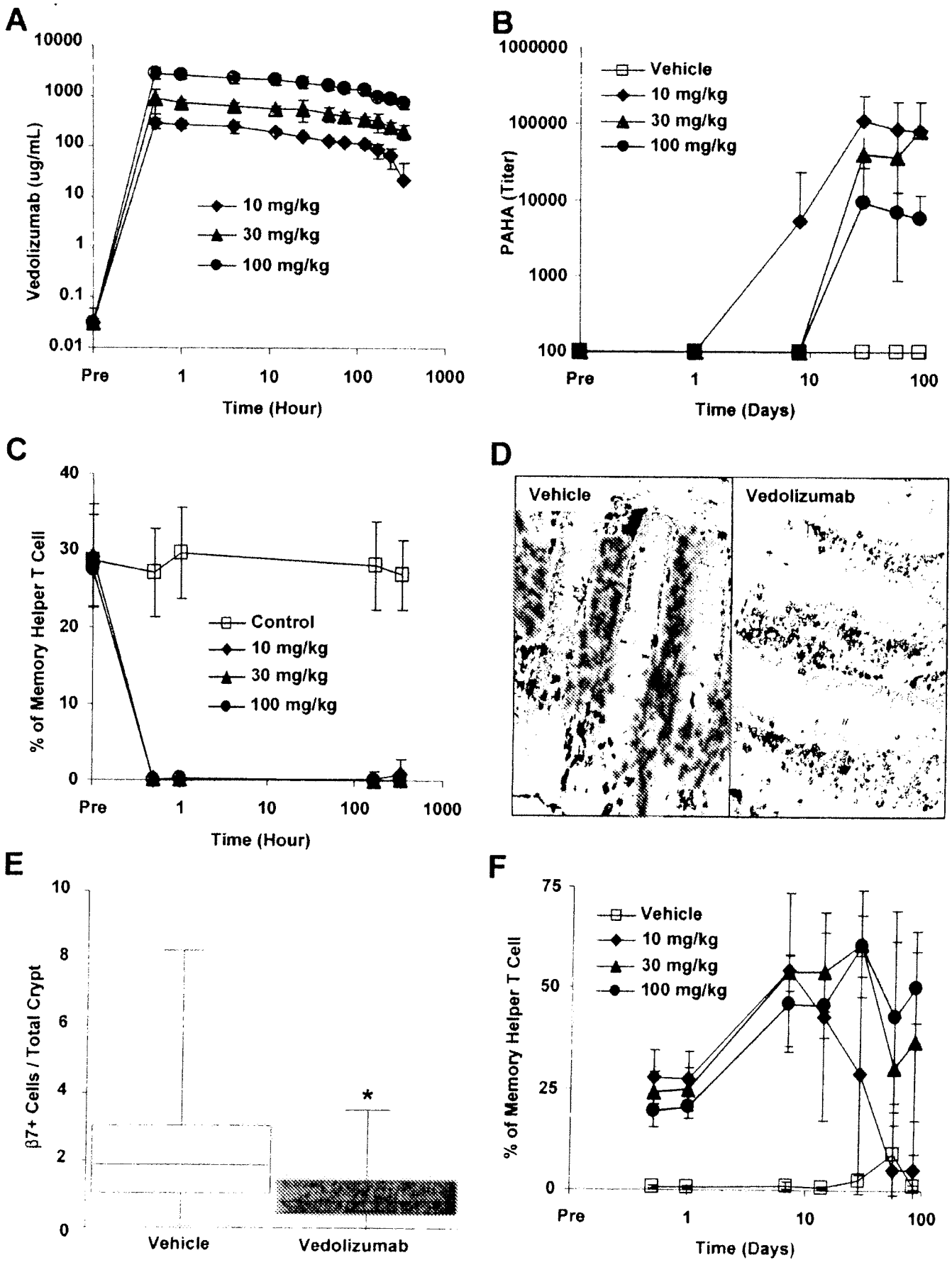

A
Vedolizumab (ug/mL)
10000
1000
100
10
1
0.1
0.01
10 mg/kg
30 mg/kg
100 mg/kg
Pre
1
10
100
1000
Time (Hour)
B
PAHA (Titer)
1000000
100000
10000
1000
100
Vehicle
10 mg/kg
30 mg/kg
100 mg/kg
Pre
1
10
100
Time (Days)
C
% of Memory Helper T Cell
40
30
20
10
0
Control
10 mg/kg
30 mg/kg
100 mg/kg
Pre
1
10
100
1000
Time (Hour)
D
Vehicle
Vedolizumab
E
β7+ Cells / Total Crypt
10
8
6
4
2
0
*
Vehicle
Vedolizumab
F
% of Memory Helper T Cell
75
50
25
0
Vehicle
10 mg/kg
30 mg/kg
100 mg/kg
Pre
1
10
100
Time (Days)

Figure 1

EXHIBIT C

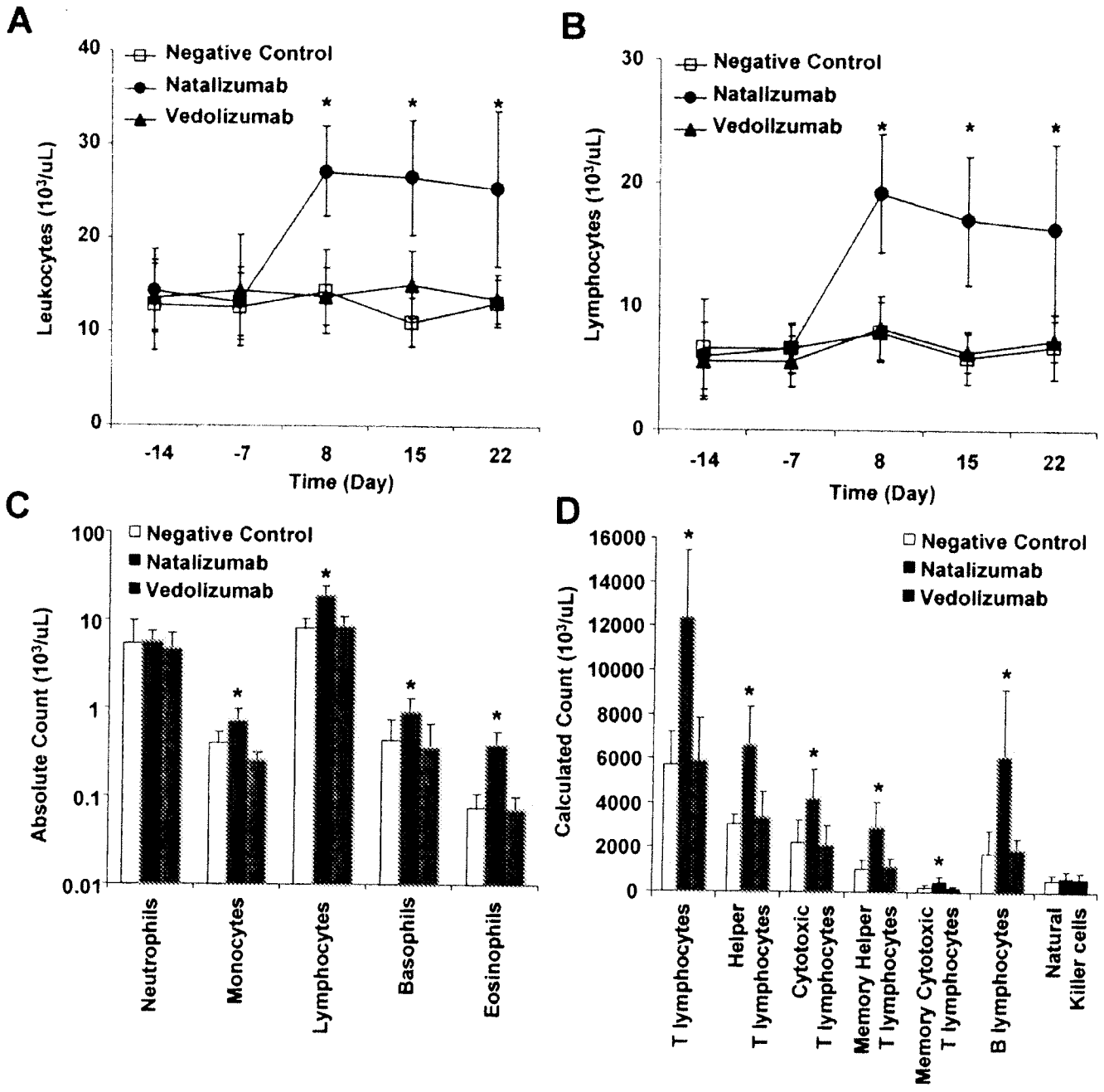

A
Negative Control
Natalizumab
Vedolizumab
Leukocytes (10³/uL)
Time (Day)
B
Lymphocytes (10³/uL)
C
Absolute Count (10³/uL)
Neutrophils
Monocytes
Lymphocytes
Basophils
Eosinophils
D
Calculated Count (10³/uL)
T lymphocytes
Helper T lymphocytes
Cytotoxic T lymphocytes
Memory Helper T lymphocytes
Memory Cytotoxic T lymphocytes
B lymphocytes
Natural Killer cells

Figure 1

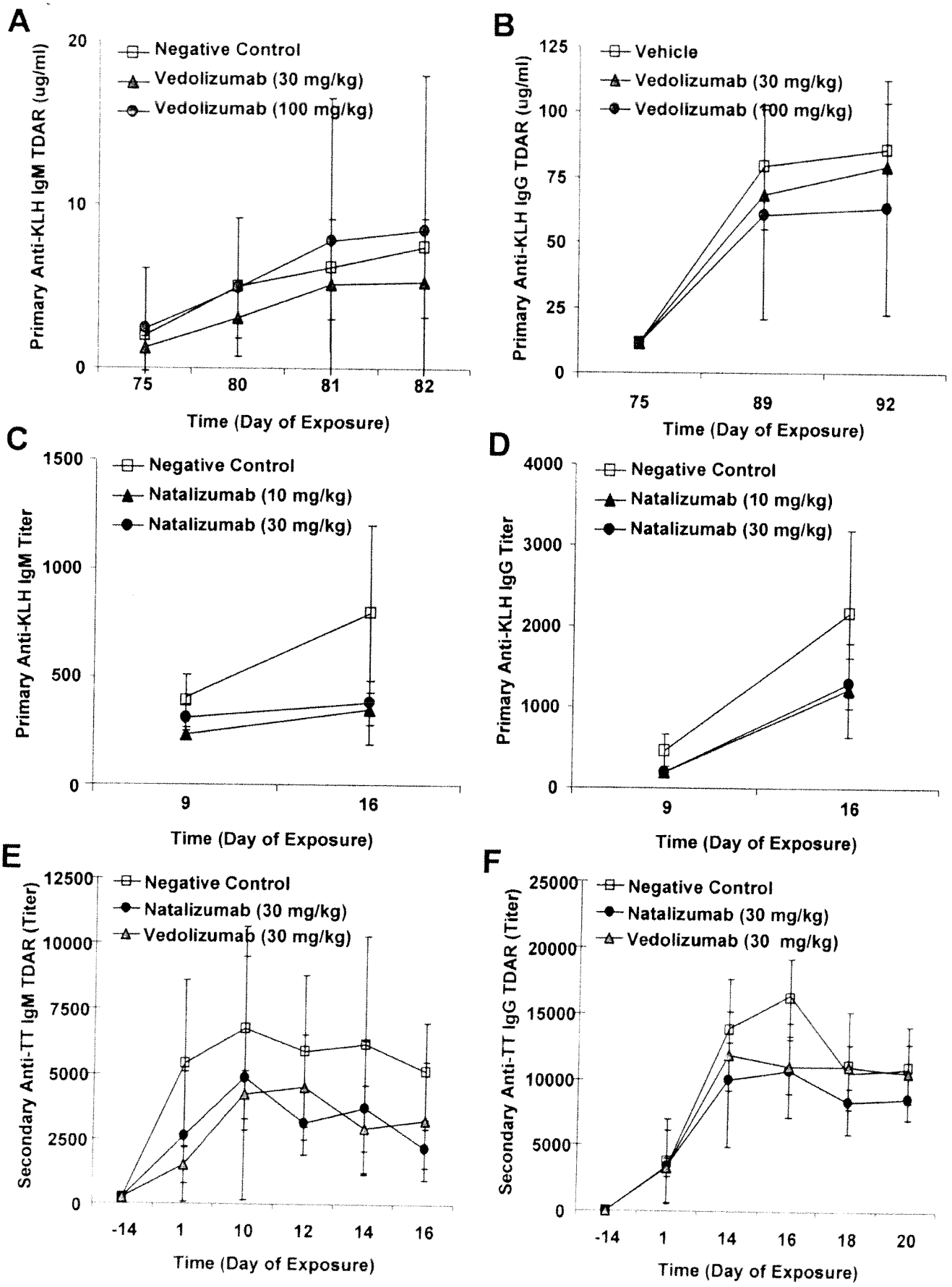

A
Primary Anti-KLH IgM TDAR (ug/ml)
20
10
0
Negative Control
Vedolizumab (30 mg/kg)
Vedolizumab (100 mg/kg)
75
80
81
82
Time (Day of Exposure)
B
Primary Anti-KLH IgG TDAR (ug/ml)
125
100
75
50
25
0
Vehicle
Vedolizumab (30 mg/kg)
Vedolizumab (100 mg/kg)
75
89
92
Time (Day of Exposure)
C
Primary Anti-KLH IgM Titer
1500
1000
500
0
Negative Control
Natalizumab (10 mg/kg)
Natalizumab (30 mg/kg)
9
16
Time (Day of Exposure)
D
Primary Anti-KLH IgG Titer
4000
3000
2000
1000
0
Negative Control
Natalizumab (10 mg/kg)
Natalizumab (30 mg/kg)
9
16
Time (Day of Exposure)
E
Secondary Anti-TT IgM TDAR (Titer)
12500
10000
7500
5000
2500
0
Negative Control
Natalizumab (30 mg/kg)
Vedolizumab (30 mg/kg)
-14
1
10
12
14
16
Time (Day of Exposure)
F
Secondary Anti-TT IgG TDAR (Titer)
25000
20000
15000
10000
5000
0
Negative Control
Natalizumab (30 mg/kg)
Vedolizumab (30 mg/kg)
-14
1
14
16
18
20
Time (Day of Exposure)

Figure 2

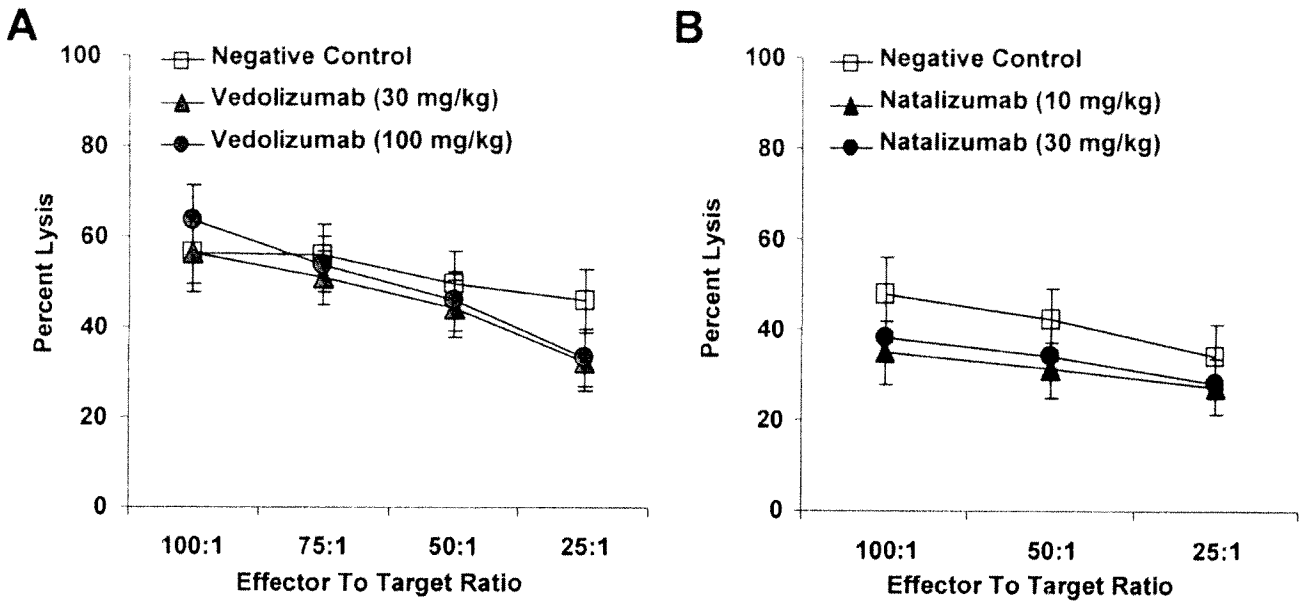

A
100
80
60
40
20
0
Percent Lysis
Negative Control
Vedolizumab (30 mg/kg)
Vedolizumab (100 mg/kg)
100:1
75:1
50:1
25:1
Effector To Target Ratio
B
100
80
60
40
20
0
Percent Lysis
Negative Control
Natalizumab (10 mg/kg)
Natalizumab (30 mg/kg)
100:1
50:1
25:1
Effector To Target Ratio

Figure 3

EXHIBIT D

Curriculum Vitae of Eric Fedyk, Ph.D.

Eric Robert Fedyk, Ph.D.

3 Whispering Way
Acton, MA 01720

(978) 263-0266
Email: fedyk@comcast.net

OVERVIEW

- A distinguished immunologist, cross-trained in inflammation, pathology, pharm- and toxicology.
- An innovative leader who transcends organizational boundaries and excels in matrix organizations.
- A versatile operations manager that has led the evolution of teams through cycles of up and down-sizing, retrofitting, retraining, etc., in efforts to meet evolving corporate needs.

PROFESSIONAL EXPEREIENCE

MILLENNIUM PHARMACEUTICALS, INC., Cambridge, MA **1999 to present**

Head of Inflammation Discovery / Director of Toxicology. (2008-present)

- Provide strategic leadership in the development for small molecule and biotherapeutic Inflammation programs to senior management of Millennium, Takeda Global Research and Development, Takeda North America and Takeda Pharmaceutical Company.
- Lead all nonclinical operations for the Inflammation portfolio, including Pre-IND, PhI, PhII and PhIII development programs, intellectual property disputes, regulatory labeling, brand development and differentiation, commercialization.
- Represent the Inflammation assets with external collaborators, regulatory agencies, patent offices, business dev. etc.
- Direct an investigational toxicology group supporting development of Takeda's Oncology franchise.
- Right-size Inflammation Discovery upon acquisition by Takeda and transfer of assets to other Takeda sites.

Associate Director, Drug Safety Evaluation (2006-2008)

- Execute regulatory and investigative toxicology studies for a small molecule inhibitor of IKK2, a small molecule antagonist of CCR9 and an anti-CCR2 therapeutic antibody.
- Direct immunotoxicology issue management activities for Pre-Clinical and Clinical Development programs, including detection of emerging bacterial and viral pathogens in response to immunosuppressive test articles.
- Represent the company's development programs with external collaborators, contract research organizations, reference laboratories, regulatory agencies and business development.
- Identify and validate genomic safety biomarkers for utilization in clinical trials and potential companion diagnostics.

Senior Scientist II, Molecular Technologies. (2004 to 2006)

- Directed operations, technology development, and staffing of a histopathology group (ex. histochemistry, ISH, IHC, IF, LCM, image analysis of frozen, FFPE and plastic sections) and an expression profiling core team (ex. RNA Isolation, cDNA, cRNA syntheses, microarray hybridization, qRT-PCR, Western).
- Directed utilization of these core technology resources by project teams representing all R&D divisions of the company.
- Identified, validated and utilized pharmacodynamic biomarkers for biotherapeutics and small molecules.
- Successfully integrated distinct departments (ex. Histopathology, Transcriptional Profiling, Protein Sciences, etc.) into a single, focused matrix organization and emerged as industry-leaders in quality and productivity.
- Invented, validated and/or implemented innovative technologies that improved data quality and/or streamlined operations.
- Increased operational efficiency by implementing process improvements and/or outsourcing.
- Improved quality via implementation of process control and standardization procedures (ex. SOPs, reference standards).

Senior Scientist I, Molecular Pathology. (2002 to 2004)

- Directed operations and staffing (≤18 FTEs) of expression profiling core teams focused on supporting biotherapeutic and small molecule projects via RNA Isolation, qPCR and slide-based assays (ISH, IHC & IF), including goal setting, performance reviews and serving as a liaison to the division executive team.
- Envisioned, developed and directed state-of-the-art, expression profiling, core platforms (e.g. sample preservation, RNA isolation, cDNA synthesis, real-time PCR) to support drug target discovery and development project teams.
- Coordinated technology development with external collaborators (ex. Applied Biosystems, EPOCH Biosciences, PreAnalytix, Qiagen, Roche Life Sciences, etc.).
- Transferred proprietary technologies to corporate partners (ex. Abbott, Aventis, Bayer, Monsanto, etc.), including training and certification.

Scientist II, Molecular Pathology (1999-2002).

- Established a state-of-the-art, RNA isolation & cDNA synthesis group and a qPCR group that drove all Target Discovery programs within Millennium.

- Lead a slide-based assay group which fueled small molecule target discovery and validation for Inflammation project teams with LCM, ISH and IHC data.

THE CENTER FOR BLOOD RESEARCH, Boston, MA **1996-1999**

Research Fellow In Pathology

- Investigated the role of chemokines, G-protein-coupled receptors and adhesion molecules in trafficking of leukocytes, in homeostatic as well as inflammatory processes.
- Trained in immunopathology, cell separation and isolation of human cells (ex. density-Ficoll-Hypaque, FACS, magnetic beads, etc.) and culture, cell adhesion and chemotaxis technologies (ex. parallel plate flow chamber, Stamper Woodruff, in vivo homing models, etc.) proteomic technologies (ex. mAb production & characterization, ELISA, flow cytometry, IHC, etc.).

THE UNIVERSITY OF ROCHESTER SCHOOL OF MEDICINE AND DENTISTRY, Rochester, NY 1990-1996

Graduate Student

- Investigated the regulation of murine B and T lymphocyte responses (ex. IgE, Th2 cytokines, etc.) by arachidonic acid metabolites (eg. prostaglandins and leukotrienes).
- Trained in isolation of leukocytes, characterization (Flow cytometry, Coulter Counter, Northerns, RNase Protection, RT-PCR, ddRT-PCR, subcloning, etc.), aseptic techniques, sterile cell culture, cell viability, activation, differentiation and viability assays (ex. MTT, XTT, proliferation, cytokine and antibody production bioassays, ELISA, ELISPOT, etc.).

LEDERLE-PRAXIS BIOLOGICALS(currently WYETH PHARMACEUTICALS), Rochester, NY 1989

Intern

- Generated and collated data describing the protective mechanism of the pediatric vaccine, Hib-TITER, which is the primary vaccine protecting infants from bacterial meningitis worldwide (*Haemophilus influenzae* type b).
- Trained in isolation of murine T cells and *in vitro* assay technologies of antigen presentation and T cell activation.

EDUCATION

Fellow	**Pathology**	**1999**	Harvard Medical School, Department of Pathology (Mentor: Timothy A. Springer).
Ph.D.	**Immunology with Honors**	**1996**	University of Rochester School of Medicine and Dentistry, Dept. of Microbiology and Immunology (Mentor: Richard P. Phipps).
M.S.	**Microbiology**	**1992**	University of Rochester School of Medicine and Dentistry, Dept. of Microbiology and Immunology (Mentor: Richard P. Phipps).
B.S.	**Biology with Honors**	**1990**	Allegheny College, Department of Biology, (Mentor: Glenn R. Wurst).

Development:

- Annual programs in operations and project management (Millennium Pharmaceuticals Inc.).
- Concepts of Project Management Course, Boston University Corporate Education Center, 2005.

Honors and Awards:

- President-elect, Phi Epsilon Sigma Chapter, Beta Beta Beta Biological Honor Society, 1988-1990.
- Best Presentation, Western Pennsylvania Sigma XI Undergraduate Research Conference, 1990.
- Alden Scholar (1987-1990), Allegheny College.
- Predoctoral Fellowship, Univ. of Rochester Sch. of Medicine. Program In Biology & Medicine, 1990.
- Predoctoral Fellowship, NIH-NIAID Pre-doctoral Research Training in Immunology, 1991-1996.
- Melvin Harer Award for Outstanding Pre-doctoral Research, 1996.
- Postdoctoral Fellowship, The Center For Blood Research, 1996-1999.
- Star Awards, Millennium Pharmaceuticals Inc.,1999-2007.
- Outstanding Contributor Award, Millennium Pharmaceuticals Inc., 2002.
- Best Abstract, Inflammatory Bowel Diseases 2010, The 5th Congress of ECCO, 2010.

Professional Associations:

- BioSafe, Society of Toxicology, Inflammation Research Association, American Association of Immunologists, American Association for the Advancement of Science, New York Academy of the Sciences.

Mentoring and Teaching Experience:

- Immunology Course Instructor, Dept. of Microbiol. & Immunol. Univ. Rochester Med. Sch. (1991-1993).
- Ph.D. Thesis committee, Massachusetts Institute of Technology, Dept. of Biol. Engineer. Arek Raczynski. 2006-present.
- Ph.D. Thesis committee, University of Massachusetts, Department of Biology, Arthur Chan, Ph.D. 2002-2005.
- Instructor for Intensive Training in Translational Medicine, The Harvard Clinical and Translational Science Center. 2010.

Advisory Boards:

- Qiagen (2002-2007).
- Cambridge Healthtech Institutue (2004-2008).
- Roche Applied Science (2006-2007).

- Oxford Global Conferences (2006-present).
- Acton Boxboro Youth Soccer (2010-present).

Editorial Boards:

- World Journal of Pharmacology (2011-2015).

SELECT SEMINARS

- **Experimental Biology 94**, Anaheim, CA, 1994. "Reactive oxygen species and not lipoxygenase products are required for mouse B lymphocyte activation and differentiation."
- **The 9th International Congress on Immunology**, San Francisco, CA, 1995. Regulation of B lymphocyte responses by E-series prostaglandins."
- **Center for Neurological Diseases, Brigham and Women's Hospital**, 1995. "Regulation of B lymphocyte responses by E-series prostaglandins and their receptors."
- **Department of Pathology, Harvard Medical School,** 1995. "Regulation of B lymphocyte responses by E-series prostaglandins and their receptors."
- **The Ernest Witebsky Center for Immunology**, State University of New York at Buffalo, 1996. "Differential display RT-PCR analysis of mRNAs which are differentially regulated by prostaglandin E receptor subtypes."
- **The Role of Chemokines in Leukocyte Trafficking and Disease**. Keystone Symposia, Copper Mnt. CO. 1997. "Domains of human CXCR4 which are required for activation by SDF-1 ."
- **Mechanisms of Leukocyte trafficking**. Keystone Symposia, Lake Tahoe, CA. 1998. "Stromal derived factor-1 (SDF-1 is a potent and efficacious chemoattractant of human B progenitor cells."
- **Chemokines and Chemokine Receptors**. Keystone Symposia, Keystone. CO. 1999. "SDF-1 is regulated by IL-1 and TNF and inhibits dermal wound healing."
- **Boston Forum in Oral and Craniofacial Biology**. Boston, MA. 1999. "SDF-1 is produced by gingival and periodontal ligament fibroblasts and production is regulated by IL-1 and TNF."
- **Biogen.** Cambridge, MA. 1999. "Anchors Away! Biological function of the homeostatic chemokine SDF-1."
- **LeukoSite Inc.** Cambridge, MA. 1999. "Anchors Away! Biological function of the chemokine SDF-1."
- **Millennium Pharmaceuticals.** Cambridge, MA. 1999. "Anchors Away! Biological function of the chemokine SDF-1."
- **23rd World Congress and Exhibition of the ISF**, UK. 1999. "Regulation of TH2 and IgE responses by PPAR- ".
- **Div. of Gastroenterology of Washington Univ.** St. Louis, MO. 2000. "Insight into IBD via TxP."
- **Cereon**, Cambridge, MA. 2001. "Focused Execution of the Gene Initiative."
- **Aventis Pharmaceuticals**. Bridgewater NJ. 2002. "High throughput RNA isolation and cDNA synthesis."
- **Qiagen Advisory Meeting.** Chatam, MA. 2002. "The Yin and Yang of high throughput transcriptomics".
- **The Bayer Research Center.** West Haven, CT. 2003. "The Yin and Yang of high throughput transcriptomics".
- **Quantitative PCR.** La Jolla, CA. 2005. Chairperson & Speaker, "Utilizing RT-qPCR to Accelerate Drug Development."
- **Chips to Hits**, Boston MA. 2005. "Assessment of RNA QC Procedures used to Make "Go/No-Go" Decisions."
- **Gene Expression Profiling to Validated Biology.** Boston, MA. October, 2005. Conference co-organizer, chairperson & speaker, "Critical factors in validating microarray data by independent technologies."
- **Roche Life Sciences Advisory Meeting,** Washington, DC. Feb. 2006. "Next-generation qRT-PCR." Speaker.
- **G.O.T. Summit.** Boston, MA. April, 2006. Chairperson & Speaker, "Quantitative PCR assays of transcript integrity predict the quality of microarray data most accurately."
- **Discovery To Diagnostics**. 2006. Technical variability in the quality of RNA extracted from formalin-fixed, paraffin-embedded tissue. Boston MA. September, Speaker.
- **Quantitative PCR, Microarrays and Biological Validation.** Strategies for Validating Transcript Data in Biopharmaceutical Development. Providence, RI. October, 2006. Conference co-organizer, chairperson & speaker.
- **Qiagen Scientific Advisory Board.** Hilden, FRG. October, 2006. "The daNorm methodology of normalizing transcript levels to endogenous references." Speaker.
- **Boston Discovery Toxicology Meeting,** Worcester, MA. November, 2006. "The TeGenero incident: Lessons learned in protein testing". Speaker.
- **Department of Pathology, Harvard Medical School.** Boston, MA. Dec, 2006. "Gene Expression In Tumors: Discovery To Diagnostics". Speaker.
- **Roche Life Sciences Advisory Meeting,** Washington, DC. Feb. 2007. "Genomic safety biomarkers." Speaker.
- **NGP Research and Development Summit,** San Juan, PR. Feb. 2007. "Challenges and opportunities in preclinical development of biomarkers." Speaker.
- **G.O.T. Summit.** Boston, MA. April, 2007. Chairperson & Speaker, "Improving Data Quality in the Development of Biopharmaceuticals."
- **Qiagen Scientific Advisory Board.** Hilden, FRG. October, 2007. "Opportunities in predictive safety biomarkers." Speaker.

- **Quantitative PCR, Microarrays and Biological Validation.** "Opportunities in predictive safety biomarkers". Providence, RI. November, 2007. Conference co-organizer, chairperson & speaker.
- **National Institute of Allergy and Infectious Diseases, National Institutes of Health**, Laboratory of Immunoregulation, "Development of MLN0002, an antagonist of the a4b7 integrin". Bethesda, MD. April, 2008. Speaker.
- **Takeda Pharmaceutical North America**. "The IBD franchise". Chicago, IL. July 2008. Speaker.
- **Takeda Pharmaceutical Company**. "Nonclinical Pharmacology of vedolizumab". Osaka, JPN. Dec 2008. Speaker.
- **Oxford Global's 3rd Annual Biomarkers Congress.** "Noninvasive biomarkers of germinal center atrophy and infection" Manchester, ENG. May 2008. Keynote speaker.
- **World Biomarker Congress.** "Safety biomarkers of germinal center atrophy and infection" Philadelphia, PA. May 2008. Chairperson and Keynote speaker.
- **Multiplexed Genomic Tools: Targeting the Missing Links Between Health and Disease.** Providence, RI. September, 2008. Conference co-organizer.
- **Biomarker Discovery Summit. "Strategies for the identification of safety biomarkers"** Philadelphia, PA. September, 2008. Chairperson and Speaker.
- **Oxford Global's 4rd Annual Biomarkers Congress.** Manchester, ENG. February 2009. Advisor and Organizer.
- **Society of Toxicology 48th Annual Meeting.** Immunoglobulin switch transcripts are non-invasive surrogate biomarkers of adaptive immune function and bacterial infection. Baltimore, MD. March 2009. Speaker.
- **TGRD Lower Gastrointestinal Tract SAB Meeting.** "Updates on MLN0002 (vedolizumab) and TAK3126". Chicago, IL. May 2009. SAB Member & Speaker.
- **Nonclinical Experts Meeting.** Preclinical development of MLN3126. Rosemont, IL. July 2009. SAB Member & Speaker.
- **The IBD Summit.** Vedolizumab MOA, Specificity and Selectivity, Integrins and Trafficking. Chicago, IL Jan, 2010.
- **Inflammatory Bowel Diseases 2010, The 5th Congress of ECCO.** The pharmacologic and toxicologic profile of the gastrointestinal-selective, anti-inflammatory therapeutic vedolizumab in nonhuman primates. Prague, CZ Feb 2010.
- **Experimental Biology 2010,** The pharmacologic and toxicologic profile of the gastrointestinal-selective, anti-inflammatory therapeutic vedolizumab in nonhuman primates. Anaheim, CA. April, 2010.
- **TGRD Vedolizumab SAB Meeting,** The gastrointestinal-selective, anti-inflammatory biologic vedolizumab. San Antonio, TX. Oct, 2010. Speaker.
- **United European Gastroenterology Week 2010,** The pharmacologic profile of the gastrointestinal-selective, anti-inflammatory drug vedolizumab in Cynomolgus macaques. Barcelona, ES. Oct, 2010. Speaker.
- **2010 Advances in Inflammatory Bowel Diseases.** The Gastrointestinal-Selective Biologic Vedolizumab Does Not Impair Immune Surveillance of the Central Nervous System in Non-Human Primates. Hollywood, FL. Dec, 2010. Speaker.
- **Inflammatory Bowel Diseases 2011, The 6th Congress of ECCO.**. The Gastrointestinal-Selective Biologic Vedolizumab Does Not Impair Immune Surveillance of the Central Nervous System in Non-Human Primates. Dublin, IRL. Feb, 2011. Speaker.

SELECT PUBLICATIONS

- Borrello, M. A., **E. R. Fedyk,** D. M. Brown and R. P. Phipps. 1993. "Strategies for studying the regulation of B lymphocytes by prostaglandin E_2". **Immunomethods**. 2:261-272.
- **Fedyk, E. R.**, M. A. Borrello, D. M. Brown and R. P. Phipps. 1994. "Regulation of B cell tolerance and triggering by immune complexes". **Chem. Immunol.** 58:67-91.
- **Fedyk, E. R.** and R. P. Phipps. 1994. "Reactive oxygen species and not lipoxygenase products are required for mouse B lymphocyte activation and differentiation". **Int. J. Immunopharmacol.** 16(7):533-546.
- **Fedyk, E. R.,** J. M. Ripper and R. P. Phipps. 1996. "A molecular analysis of PGE receptor expression by mouse B lymphocytes: coexpression of EP1, EP2, EP3 and EP4". **Mol. Immunol.** 33(1):33-45.
- **Fedyk, E. R.** and R. P. Phipps. 1996. "PGE receptors of the EP2 subtype inhibit B lymphocyte activation and proliferation while enhancing isotype switching to IgE". **Proc. Natl. Acad. Sci. USA.** 93:10978-10983.
- **Fedyk, E. R.**, A. Adawi, R. J. Looney and R. P. Phipps. 1996. "Regulation of IgE and Th2 cytokine production by cAMP and implications for extrinsic asthma". **Clin. Immunol. Immunopath.** 81(2):101-113.
- **Fedyk, E. R.**, D. M. Brown and R. P. Phipps. 1997. "PGE2 regulation of B lymphocytes and T helper 1 and T helper 2 cells: induction of inflammatory vs. allergic responses." **Adv. Exp. Med. Biol.** 407:237-42.
- **Fedyk, E. R.**, S. H. Harris, J. Padilla and R. P. Phipps. 1997. "Prostaglandin E2 receptors of the EP2 and EP4 subtypes regulate B lymphocyte activation and differentiation to IgE-secreting cells." **Adv. Exp. Med. Biol.** 433:153-7.
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